



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-N-0955]

Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Revocation of Approved Method

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order to revoke the approved method for detecting residues of carbadox, a carcinogenic new animal drug used in swine feed. An approved method is required by the Federal Food, Drug, and Cosmetic Act (FD&C Act), as implemented by regulation, to show that no residue of carcinogenic concern from a new animal drug persists in any edible tissue or in any food derived from treated animals. The approved method measures quinoxaline-2-carboxylic acid (QCA) as a marker residue to detect the presence of any residue of carcinogenic concern. QCA is a metabolite of carbadox that FDA has judged does not present a carcinogenic risk. FDA is revoking the approved method for carbadox based on its determination that the method is inadequate to monitor the residue of carcinogenic concern in compliance with FDA's operational definition of no residue because there is no established relationship between the concentration of QCA residues as measured by the approved method and the concentration of the residue of carcinogenic concern.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

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SUPPLEMENTARY INFORMATION:

I. Introduction

On July 20, 2020, FDA's Center for Veterinary Medicine (CVM), the Center within FDA that reviews and approves new animal drug applications and supplemental applications, proposed to revoke the approved method for carbadox (Ref. 1), which measures QCA as the marker residue¹ to determine whether residues of carcinogenic concern² of carbadox are present (85 FR 43853, July 20, 2020). QCA is a metabolite of carbadox that FDA has judged does not present a carcinogenic risk. The proposal to revoke the approved method was based on FDA's determination that the method does not adequately monitor the residue of carcinogenic concern in compliance with FDA's operational definition of no residue (§ 500.82(b) (21 CFR 500.82(b)(defining "no residue"; § 500.84(c)(3) (21 CFR 500.84(c)(3))). That is because the sponsor has not established the relationship between the concentration of the marker residue QCA and the concentration of the residue of carcinogenic concern.

On March 10, 2022, FDA held a public hearing under 21 CFR part 15, entitled, "Scientific Data and Information Related to the Residue of Carcinogenic Concern for the New Animal Drug Carbadox" to gather additional data and information. When FDA announced the hearing (87 FR 2093, January 13, 2022; <https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/part-15-public-hearing-scientific-data-and-information-related-residue-carcinogenic-concern-new>), we requested public comments and presentations at the public hearing, particularly: (1) on data to inform our knowledge of the residue of carcinogenic concern not summarized in the FOI Summary for the 1998 supplemental approvals, including additional data regarding the fraction of noncarcinogenic residues in the total radiolabeled residues of carbadox; (2) for any given concentration of a marker residue, the corresponding concentration

¹ See § 500.82(b) (defining "marker residue" as the residue whose concentration is in a known relationship to the concentration of the residue of carcinogenic concern in the last tissue to deplete to the S_m and defining " S_m " as the concentration of a residue of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to the human consumer).

²Consistent with FDA regulations, CVM treats unidentified residues of a carcinogenic drug as carcinogenic. See § 500.82(b) (defining "residue of carcinogenic concern" as all compounds in the total residue of a demonstrated carcinogen excluding any compounds judged by FDA not to present a carcinogenic risk).

of the residue of carcinogenic concern; (3) on additional information related to the adequacy of the current approved method to measure QCA as a marker residue for the residue of carcinogenic concern for the new animal drug carbadox not already contained in Docket No. FDA-2020-N-0955, “Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Revocation of Approved Method”; (4) on any method, other than the current approved method, that demonstrates “no residue” for the new animal drug carbadox in conformance with 21 CFR part 500, subpart E; and (5) on detailed information on the conduct and quality of studies providing data to support the points above, including information on the extraction process and the stability of residues being analyzed.

In addition to presentations from CVM and from the sponsor of the carbadox approved applications, several other stakeholders gave presentations. FDA also opened a docket (Docket No. FDA-2021-N-1326) to receive additional stakeholder comment on the topics listed above. After reviewing the comments to this docket (FDA-2020-N-0955), and presentations and the comments received in the docket for the public hearing (Docket No. FDA-2021-N-1326), FDA is now finalizing the order revoking the approved method for detecting residues of carbadox.

Elsewhere in this issue of the *Federal Register*, FDA is publishing a notice of opportunity for hearing (NOOH) proposing to withdraw approval of all new animal drug applications for use of carbadox based on the lack of an approved method for measuring the residue of carcinogenic concern. An approved method for measuring the residue of carcinogenic concern that complies with part 500, subpart E (21 CFR part 500, subpart E) is required by section 512(d)(1)(I) of the FD&C Act (21 U.S.C. 360b(d)(1)(I)).

II. Background

A. Regulation of Carcinogenic New Animal Drugs

The Delaney Clause of the FD&C Act generally prohibits the approval of carcinogenic animal drugs unless the “Diethylstilbestrol (DES) Proviso” applies. See section 512(d)(1)(I) of the FD&C Act. Under the DES Proviso exception, a carcinogenic new animal drug may be

approved if, among other things, no residue of such drug will be found by methods of examination prescribed or approved by the Secretary of Health and Human Services (HHS) by regulations in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals.

As part of a new animal drug application (NADA), the sponsor must include a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of this drug will be safe (§ 514.1(b)(7) (21 CFR 514.1(b)(7))). Carcinogenic drugs, such as carbadox, must also meet the requirements in part 500, subpart E (§ 514.1(b)(7)(ii)). These regulations, known as the sensitivity of the method (SOM) regulations, set out the requirements to demonstrate that no residues of the drug will be found by an approved method in any edible tissues of or in any foods obtained from the animal, as required to comply with the DES Proviso.

Specifically, the SOM regulations require FDA to determine if any animal drug or any of its metabolites is a carcinogen (§ 500.84(a)). For the drug and each metabolite that FDA decides should be regulated as a carcinogen, FDA calculates, based on submitted assays, the concentration of the test compound in the total diet of the test animal that corresponds to a maximum lifetime risk of cancer in the test animal of 1 in 1 million (§ 500.84(c)(1)). FDA designates the lowest concentration (i.e., the concentration of the most potent carcinogen) thus calculated as the S_o (§ 500.84(c)(1)). The S_o corresponds to a concentration of residue of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to people (§ 500.82(b)). Because FDA relies on the S_o from the most potent carcinogen, this approach ensures that use of the drug does not present a significant increase in the risk of cancer when considering all residues in edible tissues.

Because the total human diet is not derived only from food-producing animals, the SOM regulations make adjustments for human food intake of edible tissues and determine the

concentration of residue of carcinogenic concern in a specific edible tissue (such as muscle, liver, kidney, milk, or eggs) that corresponds to no significant increase in the risk of cancer to the human consumer. FDA assumes for purposes of these regulations that this value will correspond to the concentration of residues in a specific edible tissue that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million. This value is designated as the S_m (§§ 500.82(b) and 500.84(c)(1)). By limiting the concentration of residue of carcinogenic concern to a value at or below the S_m , consumers can eat a specific edible tissue every day for an entire lifetime with no significant increase in the risk of cancer.

Based on data submitted by a sponsor, FDA selects a target tissue³ and a marker residue⁴ and designates the concentration of the marker residue that the method must be able to detect in the target tissue (§ 500.86(a) through (c) (21 CFR 500.86(a) through (c))). This value, termed the R_m , is the concentration of a marker residue in the target tissue when the residue of carcinogenic concern is equal to S_m (500.82(b)). When the marker residue is at or below the R_m , the residue of carcinogenic concern in the human diet does not exceed S_o (§ 500.86(c)). This regulation ensures that when the marker residue is no longer detectable, the residue of carcinogenic concern does not exceed S_m in any of the edible tissues (§§ 500.82(b) and 500.86(c)). For any given drug, there may be several different compounds to consider for use as a marker residue. The R_m would be different depending upon the compound selected as the marker residue.

A sponsor must submit a method that is able to detect the marker residue at or below the R_m (§§ 500.88(b) (21 CFR 500.88(b)) and 500.84(c)(2)). There may be multiple methods available to detect a particular marker residue; however, under the SOM regulations, a method must be able to confirm the identity of the marker residue in the target tissue at a minimum concentration corresponding to the R_m . The Limit of Detection (LOD) for the method must be

³See § 500.82(b) (defining target tissue as the edible tissue selected to monitor for residues in the target animals, including, where appropriate, milk or eggs).

⁴See *supra* note 1 (defining “marker residue”).

less than or equal to the R_m (§ 500.84(c)(2)). FDA will determine the LOD from the submitted analytical method validation data (§ 500.88(b)).⁵ If a method is not developed that can detect the marker residue at or below the R_m , the requirements of the SOM regulations are not satisfied, and FDA cannot approve the drug (see 21 U.S.C. 360b(d)(1)(I); § 500.88).

B. History of Carbadox Approvals

Currently, there are three approved NADAs for use of carbadox in medicated swine feed, either alone or in combination with other approved new animal drugs. Carbadox, a quinoxaline derivative, is a synthetic antimicrobial used to manufacture medicated feeds that are administered ad libitum (available at all times) to swine. Phibro Animal Health Corp. (Phibro), GlenPointe Centre East, 3d Floor, 300 Frank W. Burr Blvd., suite 21, Teaneck, NJ 07666, is currently the sponsor of all three approved NADAs.

1. NADA 041-061

NADA 041-061, originally approved in 1972 (37 FR 20683, October 3, 1972), provides for the use of MECADOX 10 (carbadox) Type A medicated article to manufacture single-ingredient Type C medicated swine feeds at the rate of 10 to 25 grams per ton (g/ton) of feed for increased rate of weight gain and improved feed efficiency; and at 50 g/ton of feed for control of swine dysentery (vibronic dysentery, bloody scours, or hemorrhagic dysentery), control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *Salmonella choleraesuis*), and for increased rate of weight gain and improved feed efficiency.

⁵ As discussed above, the Delaney Clause prohibits the use of carcinogenic animal drugs unless the DES Proviso applies (see section 512(d)(1)(I) of the FD&C Act). The DES Proviso requires that, among other things, no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary of HHS by regulations) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals. FDA's SOM regulations establish the process by which a carcinogenic new animal drug may satisfy the DES Proviso. The SOM regulations were amended in 2002 to revise the operational definition of the term "no residue." Previously, FDA determined there was "no residue" in edible tissues when the concentration of the marker residue was at or below R_m . However, in 1995, the Department of Justice (DOJ)'s Office of Legal Counsel determined that FDA's interpretation was not legally supportable. Specifically, it opined that, if a method detected residue (even if the concentration of that residue fell below the R_m) the DES Proviso requirement for "no residue" was not satisfied. Accordingly, in 2002, FDA revised the definition of "no residue" to mean when the concentration of the marker residue is below the LOD of the method, meaning nondetectable by the method (67 FR 78174; see also DOJ, Mem. Op. for the Assistant Administrator & Gen. Counsel EPA & Gen. Counsel DHHS (October 13, 1995), https://www.justice.gov/d9/olc/opinions/1995/10/31/op-olc-v019-p0247_0.pdf).

In January 1998, CVM approved a supplemental application to NADA 041-061, which included the approved method (Ref. 2). However, this method was not published in the *Federal Register* as required in § 500.88, and the method that had been published for the 1972 approval was removed from the Code of Federal Regulations. Nevertheless, since the January 1998 approval of the supplemental NADA, CVM and the sponsor have treated the method approved as part of the 1998 supplemental application as the method of examination prescribed or approved by the Secretary of HHS by regulations for purposes of applying section 512(d)(1)(I) of the FD&C Act, the Delaney Clause, to carbadox.

In October 1998, CVM approved an additional supplemental NADA for NADA 041-061, changing the withdrawal period for carbadox medicated feeds from 70 days to 42 days. This supplemental NADA was approved based on the previous approval of a tolerance of 30 parts per billion (ppb) for QCA as the marker residue and a residue depletion study using the approved method that showed residues of QCA in liver depleted below 30 ppb by 42 days (Ref. 3).

2. NADA 092-955

NADA 092-955, originally approved in 1975 (40 FR 45164, October 1, 1975), provides for the use of MECADOX 10 (carbadox) Type A medicated article with BANMINTH (pyrantel tartrate) Type A medicated article to manufacture two-way, combination drug Type C medicated swine feeds at 50 g/ton of feed plus pyrantel tartrate at 96 g/ton of feed for control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery), control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *S. choleraesuis*), as an aid in the prevention of migration and establishment of large roundworm (*Ascaris suum*) infections, and as an aid in the prevention of establishment of nodular worm (*Oesophagostomum*) infections. The withdrawal period for the use of this drug combination is 70 days (§ 558.115(d)(3)(ii) (21 CFR 558.115(d)(3)(ii))).

3. NADA 141-211

NADA 141-211, originally approved in 2004 (69 FR 51173, August 18, 2004), provides for the use of MECADOX 10 (carbadox) Type A medicated article with TERRAMYCIN 50, TERRAMYCIN 100, or TERRAMYCIN 200 (oxytetracycline) Type A medicated articles to manufacture two-way, combination drug Type C medicated swine feeds at 10 to 25 g/ton of feed plus oxytetracycline at levels in feed to deliver 10 mg carbadox per pound of body weight for treatment of bacterial enteritis caused by *Escherichia coli* and *S. choleraesuis* susceptible to oxytetracycline, for treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline, and for increased rate of weight gain and improved feed efficiency. The withdrawal period for the use of this animal drug combination is 42 days (§ 558.115(d)(4); § 558.450(e)(3)(iii) (21 CFR 558.450(e)(3)(iii)).

C. Statutory Authority to Issue Order

Under 5 U.S.C. 554(e) (section 5(d) of the Administrative Procedure Act (APA)), an agency, in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty. The APA defines “order” as the whole or a part of a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rulemaking but including licensing (5 U.S.C. 551(6)). The APA defines “adjudication” as agency process for the formulation of an order (5 U.S.C. 551(7)). FDA’s regulations, consistent with the APA, define “order” to mean the final Agency disposition, other than the issuance of a regulation, in a proceeding concerning any matter (§ 10.3(a) (21 CFR 10.3(a))). Our regulations also define “proceeding and administrative proceeding” to mean any undertaking to issue, amend, or revoke a regulation or order, or to take or not to take any other form of administrative action, under the laws administered by FDA (§ 10.3(a)). Moreover, our regulations establish that the Commissioner of Food and Drugs may initiate an administrative proceeding to issue, amend, or revoke an order (§ 10.25(b) (21 CFR 10.25(b))).

On our own initiative, FDA is issuing a 5 U.S.C. 554(e) declaratory order to remove uncertainty regarding the approved method for carbadox that measures QCA as a marker residue.

An order is the most appropriate procedure to revoke the approved method because there is no rule to amend. The approved method is not currently published in the *Federal Register*, contrary to § 500.88, and the method that had been published for the 1972 approval was removed from the Code of Federal Regulations in 1998 and is no longer the approved method. The FD&C Act does not provide the procedure we must use to determine whether an approved method of examination that was never published in the Code of Federal Regulations satisfies the regulatory requirements of part 500, subpart E. Thus, we are choosing to issue a declaratory order to remove uncertainty.

III. Discussion

When CVM approved the supplemental NADA for carbadox in January 1998, it did not require the sponsor to provide data establishing a known relationship between the concentration of the marker residue (QCA) and the concentration of the residue of carcinogenic concern (§ 500.86). At that time, CVM did not believe that such information was necessary because of previous conclusions that it had made about the persistence of carcinogenic residue in the edible tissues of animals administered carbadox. CVM's understanding, at that time, was that carcinogenic residues, including desoxycarbadox (DCBX), a known carcinogenic metabolite of carbadox, depleted quickly (within 72 hours) while QCA residues depleted more slowly. However, results from subsequent studies led CVM to reexamine the conclusions it made in 1998 and conclude, based on data from these studies, that it is necessary to establish a known relationship between the marker residue and the residue of carcinogenic concern, as required by regulation.

FDA is revoking the approved method for carbadox that measures QCA as the marker residue because it is inadequate to monitor the residue of carcinogenic concern. The approved method cannot adequately monitor residue of carcinogenic concern because CVM is not aware of any data to establish a relationship between QCA and the residue of carcinogenic concern. That means that determining the concentration of QCA in animal tissue does not allow CVM to

determine whether the residue of carcinogenic concern remains in the edible tissue. Thus, the approved method does not comply with part 500, subpart E, and therefore does not satisfy the statutory requirement of section 512(d)(1)(I) of the FD&C Act.

A. CVM's Conclusions in the January 1998 Approval

In reviewing information for the supplemental NADA for carbadox in January 1998, CVM relied on studies conducted by the sponsor⁶ and academic researchers (Ref. 2) to establish an S_o and an S_m for the most potent of the carcinogenic compounds. As part of the supplemental NADA, the sponsor submitted toxicology studies, including carcinogenicity bioassays with carbadox, DCBX, and hydrazine (another carcinogenic metabolite of carbadox). These studies indicated that DCBX was the most potent of the three identified carcinogenic residues of carbadox. Based on the carcinogenicity of DCBX, CVM calculated an S_o of 0.061 ppb for residue of carcinogenic concern for carbadox in the total diet. CVM calculated an S_m value for the residue of carcinogenic concern in muscle at 0.305 ppb, in liver at 0.915 ppb, and in kidney and fat at 1.830 ppb. Because liver residues persist the longest, CVM assigned it as the target tissue. Therefore, 0.915 ppb is the S_m value for the residue of carcinogenic concern for carbadox and liver is the target tissue (Ref. 2).

Based on information submitted as part of the supplemental NADA approved in January 1998, CVM made conclusions about how long carcinogenic residues persist in the edible tissues of swine after treatment with carbadox and about the appropriate marker residue to select to monitor carbadox use. As stated in the FOI Summary for the January 1998 approval of the supplemental NADA, CVM concluded that the data:

[S]how that carbadox, desoxycarbadox and hydrazine do not persist in edible tissue as detectable residues beyond 72 hours. The agency's evaluation of these data, and the new information provided by the sponsor, demonstrate that following administration, parent carbadox is rapidly metabolized; that the metabolism of carbadox is similar among species; that the in vivo metabolism of the compounds of carcinogenic concern is also rapid and irreversible such that the resulting metabolic products cannot regenerate compounds of carcinogenic concern; that the unextractable residues are related to noncarcinogenic

⁶ Pfizer, Inc. was the sponsor for carbadox until 2001. The current sponsor is Phibro.

compounds, quinoxaline-2-carboxylic acid (QCA) and quinoxaline-2-carboxaldehyde; and that QCA is the only residue detectable in the edible tissues beyond 72 hours post dosing. Thus, the agency concludes that the unextractable bound residue is not of carcinogenic concern and that QCA is a reliable marker residue for carbadox.

CVM made the following conclusions during the review of the supplemental NADA for carbadox approved in January 1998:

1. Carcinogenic residues do not persist in animal tissue beyond 72 hours postdosing.
2. Extractable QCA is the only residue detectable in edible tissues 72 hours postdosing.
3. Unextractable residues are noncarcinogenic residues related to QCA.
4. QCA is a reliable marker residue for carbadox and its metabolites.
5. No residue of carcinogenic concern, even below the S_o , is detectable by any method after 72-hours postdosing.

Because of the conclusions made at that time, CVM did not require the sponsor to submit data to meet the requirements of the part 500, subpart E, regulations⁷ despite the fact that carbadox is a carcinogen. CVM instead established a tolerance of 30 ppb for QCA and granted the supplemental approval for carbadox.

B. The Approved Method That Measures QCA as the Marker Residue for Carbadox is

Inadequate

Under section 512(d)(1)(I) of the FD&C Act, carcinogenic new animal drugs, such as carbadox, must have a method of detection, prescribed or approved by regulation, to ensure that no residue of carcinogenic concern persists in any edible portion of the treated animals after

⁷ These regulations require the sponsor to submit data that allows FDA to designate an R_m (the concentration of the marker residue in the target tissue at which the residue of carcinogenic concern in the diet of people represents no significant increase in the risk of cancer to people) based on a known relationship between the marker residue and the residue of carcinogenic concern. In addition, the sponsor must provide a method that can detect the marker residue at or below the R_m . Under § 500.86, the necessary steps to meet the operational definition of “no residue” for carbadox are: (1) measure the depletion of the residue of carcinogenic concern until its concentration is at or below the S_m (0.915 ppb) in liver; (2) measure the depletion of the marker residue until the concentration of the residue of carcinogenic concern is at or below the S_m ; (3) use the information in (1) and (2) to establish an R_m ; and, (4) according to the regulations as they existed in 1998, develop a method that could detect the marker residue of the drug, as long as the marker residue would only be detected at or below the R_m under the proposed conditions of use. According to the current regulations, step (4) requires the development of a method that complies with the operational definition of no residue (the method’s LOD is less than or equal to the R_m and the marker residue depletes to a concentration that cannot be detected by the method).

slaughter or in any food derived from treated animals. FDA has implemented this statutory requirement through its SOM regulations in part 500, subpart E, which require that each carcinogenic new animal drug have a marker residue with a known relationship to the residue of carcinogenic concern. This relationship is necessary to establish a concentration of the marker residue (the R_m) that ensures any residue of carcinogenic concern in a specific edible tissue is below the level corresponding to maximum lifetime risk of cancer in the test animal of 1 in 1 million (the S_m), based on calculations that consider the entire human diet (the S_o). The approved method must have a limit of detection less than or equal to the R_m .

Although CVM approved the method for carbadox as part of the supplemental NADA in January 1998 and designated the S_m and S_o , it did not require the sponsor to provide data showing the relationship between QCA and the residue of carcinogenic concern and therefore could not designate an R_m . Nor did CVM require the sponsor to identify a method with a limit of detection less than or equal to the R_m . Without an R_m and an appropriate method for detecting the marker residue (i.e., a method sensitive enough to detect residues at or below the R_m), it is impossible to determine that the residue of carcinogenic concern falls below the S_m . Accordingly, based on information currently available to CVM, it is impossible to use the approved method or any other method to ensure compliance with the operational definition of no residue.

Furthermore, based on studies conducted since 1998, CVM reevaluated the conclusions that originally led it to determine that assignment of a tolerance of 30 ppb for QCA in swine liver would ensure that the residue of carcinogenic concern would remain at or below its respective S_o in all edible tissues (Refs. 4-6). Based on a review of these data, CVM concluded that: (1) carcinogenic residues persist in animal tissue more than 72 hours postdosing and (2) QCA is not the only residue detectable in animal tissue after 72 hours postdosing.

For the 2003 Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) meeting, the sponsor provided data in

which it reported that DCBX is measurable quantitatively (specific concentration measured) at 15 days postdosing (the last sampling timepoint in the study) (Refs. 4 and 5). Based on those studies, which showed the persistence of genotoxic, carcinogenic residues, JECFA recommended withdrawal of the previously established Codex Alimentarius Commission⁸ (Codex) Maximum Residue Limit (MRL). Codex subsequently agreed because the amount of residues of carbadox in human food that would have no adverse health effects in consumers could not be determined. Following that meeting, the Codex Committee on Residues of Veterinary Drugs in Foods withdrew the MRL for carbadox (Ref. 7). Carbadox has been removed from the market in many foreign jurisdictions, including the European Union (Ref. 8), Canada (Ref. 9), and Australia (Ref. 10).

In 2005, the sponsor provided CVM with summary reports for the studies evaluated by the 2003 JECFA. CVM responded later that year, informing the sponsor that: (1) because the summaries indicated that carcinogenic residues persist longer than previously known and there is no established relationship between QCA and the residue of carcinogenic concern, CVM was concerned that the use of the 30 ppb tolerance for QCA and the use of QCA generally as a marker residue may not be appropriate and (2) accordingly, the sponsor would need to submit existing or new studies to address the relationship of QCA at 30 ppb and the residue of carcinogenic concern. CVM also told the sponsor that, if it was determined that QCA is not appropriate as the marker residue, the sponsor would need to conduct additional metabolism and residue depletion studies to identify an appropriate marker residue and tolerance in order to maintain the carbadox approvals.

Between 2005 and 2011, CVM continued to meet with the sponsor and to review various submissions from the sponsor, including but not limited to a study the sponsor conducted in 2008 to 2009 and submitted in 2009 (hereinafter “the 2008 study”). None of the submissions, however, contained reports of studies that were designed to generate the needed information.

⁸ For more information about Codex, see <https://www.fao.org/fao-who-codexalimentarius/committees/cac/about/en/>.

Therefore, in 2011, pursuant to section 512(l)(1) of the FD&C Act, FDA ordered the sponsor to provide FDA with all data, studies, analyses, reviews, reports, or other scientific evaluations in its possession related to the persistence of DCBX in edible tissues, the appropriateness of QCA as an analyte for residue monitoring and for establishing a withdrawal time for the use of carbadox in pigs, and whether an analytical method for monitoring carbadox-related carcinogenic residues in edible tissues can be developed that would comply with part 500, subpart E. The sponsor responded with, among other submissions, the complete study reports for the studies evaluated by the 2003 JECFA. CVM reviewed the reports and determined that the data show qualitatively (specific concentration not measured) that carbadox and DCBX are present in liver tissue samples at 48 hours and at 15 days withdrawal, respectively. For samples exposed to enzymes to mimic human digestion, CVM concluded that the mass spectrometry chromatograms and the reported DCBX concentration data provide qualitative confirmation of the presence of DCBX at 15 days withdrawal. These reports show that the known carcinogenic residues (DCBX) persist beyond 72 hours and that QCA is not the only residue detectable after 72 hours.

In response to CVM's proposal to withdraw approval of the carbadox containing new animal drug applications in 2016,⁹ the sponsor submitted reports from six studies (hereinafter "the 2016 studies"). These studies, some of which began in 2012, were initiated without agreement from CVM that they would provide the necessary data to address CVM's concerns (specifically, data to demonstrate that the approved method was adequate to measure the residue of carcinogenic concern in compliance with FDA's SOM regulations, or that an alternative method to do so was available).

⁹ CVM issued a Notice of Opportunity for Hearing (NOOH) on a proposal to withdraw approval of the carbadox containing NADAs on April 12, 2016. [81 FR 21559; (Correction published on April 21, 2016 (81 FR 23499), to correct the telephone number for the individual to be contacted for further information. The address for Phibro Animal Health Corp. was also corrected.)] Phibro submitted data from the 2008 study in its Request for a Hearing in response to the NOOH. [<https://www.regulations.gov/document/FDA-2016-N-0832-0029>] Phibro also submitted to that same docket reports from additional studies in July 2016. CVM withdrew the 2016 NOOH on July 20, 2020 (85 FR 43852).

Finally, the sponsor and others submitted presentations, documents, and information in response to the 2020 proposed order, at the March 10, 2022, public hearing, and/or to the docket for the public hearing. CVM reviewed the presentations, documents, and information, and determined that they were not sufficient to establish a relationship between QCA and the residue of carcinogenic concern, which includes carbadox and DCBX. Additionally, there were no data to establish the residue level of QCA at which the residue of carcinogenic concern in the diet of people represents no significant increase in the risk of cancer to people. Without these data, CVM cannot establish the R_m and the sponsor cannot demonstrate “no residue” of carcinogenic concern as required by the SOM regulations in part 500, subpart E, which implement the FD&C Act at 21 U.S.C. 360b(d)(1)(I).

In sum, based on review of data submitted following the 1998 approval of the method, CVM concludes that: (1) carcinogenic residues persist in animal tissue more than 72 hours postdosing and (2) QCA is not the only residue detectable in animal tissue after 72 hours postdosing. CVM also concludes that data and information submitted since 1998, including to this docket and to Docket No. FDA-2021-N-1326 by the sponsor and others, do not provide information needed to establish the relationship between QCA and the residue of carcinogenic concern. Without knowing this relationship and without a method for measuring a marker residue with a limit of detection at or below the R_m , the approved method is inadequate for monitoring compliance with FDA’s operational definition of no residue (see § 500.84(c)(3)). Accordingly, the approved method for carbadox does not satisfy the statutory or regulatory requirements and is being revoked.

IV. Comments Received on the Proposed Order and Public Hearing

A. Comments Submitted by the Sponsor

The sponsor of the carbadox NADAs submitted information to the docket of the proposed order, presented information at the public hearing, and submitted information to the docket for that hearing. CVM’s scientific review of the sponsor’s submitted data, analysis, and comments

prior to the hearing is discussed below and in “CVM Response to Phibro Animal Health Corporation’s September 18, 2020 Comments on CVM’s July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox” (January 6, 2022), which was posted to the public docket before the hearing (Ref. 6). Information submitted during or after the hearing is discussed below and in “CVM’s review of documents Phibro submitted to Docket No. FDA-2021-N-1326 and presentation at the March 10, 2022 Part 15 Hearing” (October 30, 2023) (Ref. 11), and “CVM review of comments on the Zhang Article that Phibro references in the document submitted to the Part 15 Hearing docket under cover letter dated June 9, 2022, and entitled, ‘Phibro Animal Health Corporation’s Reply to the January 6, 2022 “CVM Response to Phibro Animal Health Corporation’s September 18, 2020 Comments on CVM’s July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox” ’” (October 30, 2023) (Ref. 12). CVM’s review of the sponsor’s procedural and policy objections is reflected below and in the denials of the sponsor’s citizen petition (Docket No. FDA-2020-P-2312) and petition for stay of action (Docket No. FDA-2020-P-2313), available at <https://www.regulations.gov>.

In the sponsor’s comments and oral presentation, it argued that QCA is an adequate marker residue and defended the approved method, which measures QCA. The comments defended the use of the 30 ppb QCA tolerance and 42-day withdrawal period as sufficient to protect human and animal safety. The sponsor alternatively suggested use of the U.S. Department of Agriculture Food Safety and Inspection Service (FSIS) method to measure QCA. The sponsor also proposed that DCBX could be used as a marker residue. For measuring DCBX, the sponsor proposed the Canadian Food inspection Agency (CFIA) method. The sponsor also suggested that other unnamed methods were available. Finally, the sponsor argued that a final order was not the appropriate process to revoke an approved method and that an NOOH is required instead.

Comment on use of QCA as a marker residue. The sponsor states that an R_m can be calculated for QCA based on the available data and submitted an expert opinion about the R_m for

QCA. By analyzing QCA and DCBX concentrations, the sponsor's expert states that the R_m for QCA is either 28.49 ppb (using the 2008 study data and the approved method) or 28.61 ppb (using the data submitted for the 1998 supplemental approval and the approved method). The sponsor also asserted that even if DCBX residues persist longer than previously known, no residue of carcinogenic concern persists beyond the current 42-day withdrawal period. The sponsor stated that either the approved method or FSIS method could be used to measure QCA.

Response to use of QCA as a marker residue. After reviewing the sponsor's studies submitted to the 2003 JECFA, the 2008 study, the 2016 studies, and other comments and analyses provided by the sponsor, CVM concludes that it lacks the data to establish an R_m for QCA or any other marker residue. The sponsor's expert opinion estimated the concentration of QCA when DCBX is 0.915 ppb (the S_m for the residue of carcinogenic concern in liver for carbadox). This analysis relied solely on residues of DCBX instead of considering the residue of carcinogenic concern. DCBX is only one metabolite of carbadox and therefore just one component of the residue of carcinogenic concern, which includes all compounds in the total residue of a demonstrated carcinogen excluding any compounds judged by FDA not to present a carcinogenic risk (§ 500.82). Because QCA and another metabolite, methyl carbazate, are the only compounds of carbadox that FDA has judged to not present a carcinogenic risk, the residue of carcinogenic concern for carbadox includes all carbadox residues except for QCA and methyl carbazate. The sponsor did not provide an R_m for the marker residue QCA that accounted for the residue of carcinogenic concern, nor is CVM able to calculate one based on the data available. Without an R_m , CVM cannot determine if the approved method, FSIS method, or any other method that measures QCA as the marker residue is sufficiently sensitive to satisfy the regulatory and statutory requirements.

Contrary to the sponsor's assertion that the residue of carcinogenic concern does not persist beyond the 42-day withdrawal period, data quantifying the residue of carcinogenic concern for carbadox from the 1998 supplemental approval indicates that a marker residue would

exceed the R_m (the concentration associated with no increase in risk to the human consumer) more than 70 days post-dosing. The data submitted for the 1998 supplemental approval showed that the total radiolabeled residues have a concentration of 13.3 ppb at 70 days post-dosing, the last timepoint in the study. After removing the 9.9 percent QCA residues detected at 70 days,¹⁰ the remaining residue has a concentration of 11.98 ppb. This concentration far exceeds the S_m value of 0.915 ppb for carbadox and therefore these data cannot be used to calculate an R_m . At most, these data indicate that a marker residue would not reach the R_m until more than 70 days post-dosing, well past the current 42-day withdrawal period.

The sponsor's 2008 study and 2016 studies did not provide the information to determine the residue of carcinogenic concern. The sponsor's 2008 study does not provide information on the residue of carcinogenic concern because it measured only QCA and DCBX, not total residues of carbadox. In addition, CVM concluded that the data from that study cannot be considered quantitative because of poor method performance. Likewise, the sponsor's 2016 studies do not provide quantitative data on the residue of carcinogenic concern. Additionally, although the sponsor attempted to separate the residues and measure the presence of each compound individually, it failed to demonstrate that the analytical procedures used did not cause carcinogenic compounds to degrade to noncarcinogenic compounds. CVM's review of the method performance issues and analytical flaws in the sponsor's studies is discussed in greater detail in Refs. 6 and 11.

CVM also reviewed the information provided by the sponsor during the public hearing and to the docket following the hearing and concluded that such information does not allow CVM to determine an R_m for the approved method. The new information concerns the procedures, analysis, and documentation for the 2016 studies; however, none of the new information provides the data necessary to calculate an R_m because the studies were not designed

¹⁰ According to the 1998 FOI Summary, QCA and methyl carbazate are noncarcinogenic metabolites of carbadox (Ref. 2). The sponsor provided quantitative measurements for QCA, but not for methyl carbazate.

to generate the quantitative data necessary to make these calculations. CVM's review of the new information is discussed in greater detail in Ref. 11.

Comment on use of DCBX as a marker residue. The sponsor proposed the use of DCBX as a marker residue and suggested the CFIA method for detecting DCBX. According to an expert opinion submitted by the sponsor, DCBX depletes to a concentration of 0.915 ppb at approximately 23 days post-dosing and depletes to the 0.015 ppb detection limit for the CFIA method at 75 days post-dosing.

Response to use of DCBX as a marker residue. Because DCBX is only part of the residue of carcinogenic concern, the sponsor's expert opinion and analysis are insufficient to ensure compliance with the SOM regulations. The residue of carcinogenic concern for carbadox includes all carbadox residues excluding residues judged by FDA not to present a carcinogenic risk (§ 500.82(b)). For carbadox, only the compounds QCA and methyl carbazate have been judged by FDA to be noncarcinogenic. All other compounds cannot be excluded from the residue of carcinogenic concern. At most, the expert's opinion indicates that the concentration of the residue of carcinogenic concern would reach the S_m at some point after 23 days (since DCBX is only part of the residue of carcinogenic concern) and that detectable residues of a carcinogenic new animal drug are present at 75 days post-dosing, which is 33 days longer than the current withdrawal period and 72 days longer than was known in 1998. This information is insufficient to determine an R_m for DCBX as a marker residue. Without an R_m , CVM cannot determine if the CFIA method or any other method to measure DCBX is sufficiently sensitive to satisfy the regulatory and statutory requirements (§ 500.88(b)).

Comment on carbadox metabolism. During the public hearing, the sponsor stated that the metabolism for carbadox is well-known and asserted that carbadox depletes to DCBX, which in turn depletes to the noncarcinogenic QCA. The sponsor addressed an April 2022 study (Ref. 13) about the metabolism and residue depletion of carbadox and asserted that compounds other than

DCBX and QCA are intermediates that are present “only fleetingly.” The sponsor also stated during the public hearing that it would be willing to conduct additional studies.

Response on carbadox metabolism. CVM reviewed the sponsor’s comments regarding a study published in April 2022 that describes metabolism and residue depletion of carbadox (Ref. 12). The study identified eight different metabolites of carbadox (DCBX, QCA, and six others) and proposed two different metabolic pathways for the degradation of carbadox. The study contradicts the sponsor’s claim that DCBX represents the entirety of the residue of carcinogenic concern. Although the sponsor states that the six non-QCA, non-DCBX carbadox residues identified in the April 2022 study are present “only fleetingly,” the method used in that study was not capable of detecting carbadox metabolites below 20 ppb, a concentration far greater than the S_m . Further, FDA regulations prohibit us from excluding compounds from the residue of carcinogenic concern until they have been judged to be noncarcinogenic. Only compounds known to be noncarcinogenic can be subtracted from the total residues for the determination of residue of carcinogenic concern. Although the 2022 study adds to our knowledge about previously unidentified carbadox residues, it does not provide total residue data that could be used to calculate the residue of carcinogenic concern or to determine a relationship between a marker residue and the residue of carcinogenic concern for establishment of an R_m . Finally, although the sponsor stated that it would be willing to conduct additional studies, it has not submitted additional studies to date.

Comment on process to revoke the method. The sponsor also argued that CVM cannot lawfully revoke an approved method using a final order under the FD&C Act and its implementing regulations, agency precedent, the Administrative Procedure Act, and the Due Process Clause of the U.S. Constitution and must rely instead on an NOOH and an evidentiary hearing before an impartial adjudicator to address the adequacy of the approved method. Alternatively, the sponsor asserted that revocation of the method requires rulemaking under the APA instead of a declaratory order. The sponsor also argued that it is arbitrary and capricious to

revoke an approved method without establishing an alternative method and that a public hearing is not a substitute for a formal evidentiary hearing.

Response on process to revoke the method. It is appropriate under the FD&C Act and its regulations, agency precedent, the Administrative Procedure Act, and the Due Process Clause of the U.S. Constitution to address the adequacy of the approved method through a declaratory order as a threshold matter before proceeding to an NOOH on withdrawal of the drug's approval. Although the FD&C Act requires an opportunity for a hearing prior to withdrawing an animal drug approval (which FDA is providing by issuing an NOOH and considering any request for hearing it receives), the FD&C Act does not require a specific procedure to determine whether a particular method of examination satisfies the statutory and regulatory requirements, nor does it address the situation when an agency did not follow a regulatory requirement to publish that method in the *Federal Register*. A declaratory order is an appropriate process under the FD&C Act and APA to determine whether a statutory exclusion applies. *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 626 (1973) (holding that FDA could issue a declaratory order to terminate controversy and remove uncertainty regarding whether a new drug and "me-too" drugs were exempt from providing efficacy data).

In *Weinberger*, the Supreme Court agreed with FDA's conclusion that efficacy data was required for a class of drugs but held that a hearing was necessary before withdrawal because the drug sponsor had submitted substantial evidence of efficacy in line with FDA's regulatory requirements for well-controlled studies. *Id.* at 622-23. Here, FDA concludes that the approved method, which relies on a tolerance of 30 ppb for QCA, does not comply with the statute and implementing regulations because there is no R_m for the marker residue QCA and no determination that the approved method is sufficiently sensitive to detect the marker residue at or below the R_m . Unlike the situation in *Weinberger*, where the drug sponsor submitted efficacy data in line with the regulatory and statutory requirements, the drug sponsor does not assert here that the current tolerance of 30 ppb for QCA has a known relationship with the residue of

carcinogenic concern and therefore has not submitted evidence that the approved method satisfies the statutory and regulatory requirements. Instead, the drug sponsor's expert states that the R_m for QCA is either 28.49 ppb (using the 2008 data and the approved method) or 28.61 ppb (using the data submitted for the 1998 supplemental approval and the approved method) based on a calculation that estimates concentrations of QCA when the estimated concentration of DCBX is 0.915 ppb. DCBX is not the only carcinogenic residue that must be considered when determining an R_m , so the sponsor's calculations do not account for the entire residue of carcinogenic concern. However, even if we were to assume that DCBX is the only carcinogenic residue present, the sponsor's assertion essentially admits that its own expert does not think the current tolerance satisfies the regulatory requirements because the current tolerance of 30 ppb is more than 28.49 ppb or 28.61 ppb (the R_m identified by the sponsor's expert).

Currently, edible tissues may enter the food supply if they contain a concentration of QCA at or below 30 ppb. According to the expert's calculation, when QCA is more than 28.49 ppb or 28.61 ppb, edible tissues would still contain carcinogenic DCBX above 0.915 ppb, the level that corresponds to no significant increase in the risk of cancer to the human consumer. If we accept the expert's calculations as true,¹¹ edible tissues with a QCA concentration of 29 ppb, for example, could contain carcinogenic residues above 0.915 ppb, yet those edible tissues could enter the food supply because the QCA tolerance would be satisfied. The sponsor argues that the current 42-day withdrawal period provides an additional margin of safety sufficient to meet the statutory and regulatory requirements because the sponsor's expert estimates that DCBX depletes to 0.915 ppb at 23 days, 19 days before the end of the withdrawal period. However, edible tissues are analyzed for residue concentrations; the length of time since the animal was treated is not measurable from tissue analysis. Thus, safety is assured by measuring the concentration of a marker residue that tracks the residue of carcinogenic concern in edible tissues

¹¹ As discussed above, DCBX is not the only residue of carcinogenic concern and we have concerns regarding the quality of data from the 2008 study.

to determine whether the concentration is below or above the R_m . Regardless of the length of the withdrawal period, the “no residue” requirement cannot be met if the marker residue is above the R_m . Even if we accepted the sponsor’s calculations as true, a tolerance of 30 ppb for QCA would not be at or below the R_m (calculated by the sponsor’s expert as 28.49 ppb or 28.61 ppb) in edible tissues of treated swine. Thus, even the sponsor’s own expert opinion supports FDA’s conclusion that the approved method does not satisfy the statutory and regulatory requirements.

CVM spent a decade (2005 to 2015) in discussions with the sponsor regarding the data necessary to identify an adequate method and did, and continues to, invite the sponsor to provide that data. At this time, as discussed above, the sponsor has not submitted that data.

The method revocation and withdrawal of NADA approvals are not so intertwined as to require a hearing on revocation under the statute or FDA’s regulations. While a sponsor may have an opportunity at a hearing held on either NADA approvability or NADA withdrawal to show whether there is an approvable method to meet the DES Proviso, the FD&C Act does not require an opportunity for a hearing on the interlocutory revocation of an approved method. 21 U.S.C. 360b(c)(1) and (e)(1)(B). Furthermore, CVM’s decision to revoke the method separately from (and before) taking action on the NADA is consistent with D.C. Circuit opinions regarding the DES withdrawal proceedings, which declined to apply the Delaney Clause when there were currently approved methods that did not result in detectable levels of residue. In *Hess & Clark, Division of Rhodia, Inc. v. FDA*, 495 F.2d 975 (D.C. Cir. 1974), and its companion case, *Chemetron Corp. v. U.S. Dep’t of Health, Educ. & Welfare*, 495 F.2d 995 (D.C. Cir. 1974), the court overturned FDA’s withdrawal of approvals of DES because it held that the NOOH preceding the withdrawals did not adequately provide notice and a meaningful opportunity to respond to test results that FDA claimed supported withdrawal. *Hess & Clark*, 495 F.2d at 983; *Chemetron*, 495 F.2d at 999. Notably, the test results were from a method that the U.S. Department of Agriculture (USDA) utilized that was different from the approved methods for DES. In discussing the USDA method, the court stated that “the Delaney Clause is plainly

inapplicable” where “the only method by which residues have been detected is [an unapproved method].” *Hess & Clark*, 495 F.2d at 991; *see also Chemetron*, 495 F.2d at 999 (“The ‘DES’ exception to the Delaney Clause...continues effective unless the agency detects residues in a slaughtered animal while using an approved test method. And the residues detected by [USDA] were not found by an ‘approved method.’ ”). Under this logic, the Delaney Clause will only apply after the approved method has been revoked or residue is found by the approved method. Consistent with these cases (the only court cases that address the applicability of the Delaney Clause when there is still an approved method), CVM is addressing the adequacy of the approved method for carbadox before relying on the Delaney Clause to take action to withdraw the NADAs.¹² FDA’s decision to revoke the approved method relies on the information submitted to date by the drug sponsor. This revocation does not prevent the drug sponsor from providing new or additional data to establish an R_m for a marker residue in accordance with the statute and regulations.

On the two previous occasions when FDA withdrew approval for carcinogenic animal drugs (DES and a class of drugs called “nitrofurans”), FDA relied on both the Delaney Clause and the general safety clause, so these prior situations differ significantly from a withdrawal based solely on the Delaney Clause. Furthermore, both sets of withdrawal proceedings began before FDA finalized the SOM regulations in 1987 and therefore provide no guidance on the appropriate process to determine whether a method complies with the SOM regulations. The SOM regulations (which implement the DES Proviso) are a rule of general applicability because they set forth the general requirements for all regulatory methods for carcinogenic new animal drugs; by contrast, this final order revoking the method is appropriate as a declaratory order because it determines whether one specific method satisfies these general requirements.

¹² While, subsequent to the 1974 DES decisions, FDA proceeded to a hearing on the withdrawal of DES without revoking the method first, FDA relied on both the general safety clause and the Delaney Clause as the basis for withdrawal and, upon subsequent challenge, the D.C. Circuit declined to address FDA’s application of, or procedure regarding, the Delaney Clause. *Rhone-Poulenc, Inc., Hess & Clark Division v. FDA*, 636 F.2d 750, 751-52 & n.2 (D.C. Cir. 1980).

Notably, FDA does not approve regulatory methods through notice-and-comment rulemaking under the APA. *See* 76 FR 72617, November 25, 2011 (publishing regulatory method to detect residues of carcinogen without notice-and-comment rulemaking). Because notice-and-comment rulemaking is not required to publish a regulatory method, it is not required to revoke a regulatory method. *See Perez v. Mortg. Bankers Ass’n*, 575 U.S. 92, 101 (2015).

CVM provided notice of the proposed order and a meaningful opportunity to be heard. The drug sponsor and other interested parties had an opportunity to provide comments and other information. The public hearing served as an additional opportunity for the sponsor and the public to comment on this matter. The sponsor presented orally and submitted additional comments to the public hearing docket. In addition, the sponsor remains able to market carbadox lawfully, so the sponsor has not been deprived of a property right.

CVM, as the component of FDA charged with applying the Delaney Clause and DES Proviso, is appropriately advising on this order and its involvement does not infect any subsequent proceedings with any bias. Elsewhere in this issue of the *Federal Register*, FDA is publishing an NOOH and, pursuant to FDA regulations, were the sponsor to request a hearing, the adjudicator of that request would be affiliated with FDA’s Office of the Commissioner and would have had no previous role in the proceedings to date.

Comment on policy considerations. The sponsor asserts that revoking the approved method for carbadox and the resulting withdrawal of carbadox, if it were to occur, would be poor policy because carbadox supports animal health and serves the public interest in preventing antimicrobial resistance and because the swine industry and U.S. economy would face significant costs following revocation of the method and/or withdrawal of approval of the NADAs. The sponsor also asserts that carbadox is safe in that it has been used for over 50 years and has not been linked to a single instance of cancer in pigs or humans.

Response to comment on policy considerations. These comments are not relevant to whether the approved method meets our regulatory requirements and is adequate to monitor the

residue of carcinogenic concern in compliance with FDA’s operational definition of no residue or provide information needed to establish the relationship of QCA to the residue of carcinogenic concern. Without an adequate method, the drug cannot meet the DES Proviso in section 512(d)(1)(I) of the FD&C Act that permits the approval of carcinogenic animal drugs under certain conditions. The carcinogenicity studies of carbadox provided clear evidence that carbadox caused cancer in mice and rats under laboratory conditions; therefore, the Delaney Clause applies because “such drug induces cancer when ingested by man or animal.” 21 U.S.C. 360b(d)(1)(I).

CVM considered the sponsor’s other comments and concluded that they were not relevant to determining whether the approved method, the CFIA method, the FSIS method, or any other method complies with the regulatory and statutory requirements. The comments are discussed in greater detail in CVM’s memoranda regarding carbadox (Refs. 6, 11, and 12) and denials of the sponsor’s citizen petition (Docket No. FDA-2020-P-2312) and petition for stay of action (Docket No. FDA-2020-P-2313). Based on the available evidence, there currently is no analytical method for which CVM can conclude that the SOM regulations are met, nor has the sponsor provided the data to establish an R_m for any marker residue. Without this information, CVM is unable to conclude that there is no residue of carcinogenic concern in swine treated with carbadox.

B. Comments Submitted by Other Stakeholders

The non-sponsor comments submitted to this docket and to Docket No. FDA-2021-N-1326, and non-sponsor presentations at the part 15 hearing, generally concerned the need for carbadox for animal health and projected economic losses to the swine industry from a decrease in animal health; the increase in the use of medically important antimicrobials if carbadox were no longer available; human food safety and environmental safety; and requests for FDA to work with the sponsor to develop and approve an adequate method. However, none of the non-sponsor comments contained any data or information demonstrating that the approved method

meets our regulatory requirements and is adequate to monitor the residue of carcinogenic concern in compliance with FDA's operational definition of no residue or that a different method meets the requirements.

Comments on animal health and projected economic losses to the swine industry. FDA received several comments stating that carbadox is the only effective option for stopping swine dysentery and that alternatives (including vaccines) either do not exist or do not work as well. Several comments indicated that removing carbadox from the market would lead to animal suffering and death, and several cited a survey of veterinarians conducted in 2016 and again in 2020 that estimates the removal of carbadox would result annually in sickness for 53.5 million otherwise healthy pigs and cost the nation's hog industry \$5.3 billion over the next decade. Other comments noted that the approved uses of carbadox are limited to growth promotion, the control of swine dysentery, and control of salmonellosis caused by *Salmonella choleraesuis*. A comment stated that swine dysentery and *S. choleraesuis* are rare in U.S. swine herds and can be managed without antibiotics, pointing to countries that have banned the use of carbadox.

Comments on antimicrobial resistance. Some comments stated that the only alternatives to carbadox that could be used to treat swine dysentery are medically important antibiotics for humans, such as aminoglycosides, and that removing carbadox is contrary to FDA's strategy with respect to antimicrobial resistance. We also received comments stating that research has shown that the use of carbadox in swine increases gene transfer, creating its own resistance problems.

Comments on human food safety and environmental safety issues. We received several comments defending the human food safety of swine administered carbadox. One comment pointed out that *Salmonella* is zoonotic and could result in food safety issues if not controlled and that there is an expectation that *Salmonella* and *Brachyspira* would make their way into slaughterhouses, potentially resulting in lower meat quality and increased contamination if carbadox is no longer available. We also received comments that asserted that the use of

carbadox creates dangerous residues in food products and results in residues of carbadox and its metabolites in surface waters in states with large numbers of pig-producing facilities, and that carbadox poses allergen and genotoxicity hazards to the farm and feed mill workers who handle products containing the drug.

Response to comments on animal health, industry economic losses, antimicrobial resistance, and human food safety. These comments are not relevant to whether the approved method meets our regulatory requirements and is adequate to monitor the residue of carcinogenic concern in compliance with FDA's operational definition of no residue or provide information needed to establish the relationship of QCA or any other marker residue to the residue of carcinogenic concern. Without an adequate method, the drug cannot meet the provisions of section 512(d)(1)(I) of the FD&C Act.

Comments on process to develop a new method. Several comments requested that FDA work with the sponsor to develop and approve a new method. Comments also presented the view that FDA did not provide the sponsor of carbadox with a clear path forward and that FDA diverged from its established process, urging that FDA work with the sponsor or publish an NOOH regarding the adequacy of the approved method.

Response to comments on process to develop a new method. Before publishing the proposed order, CVM worked with the sponsor for many years (from 2005 to 2015), during which time it described the steps needed to be completed to obtain the necessary data to establish an R_m . CVM has repeatedly requested data from the sponsor to establish the relationship between QCA and the residue of carcinogenic concern. During this time, the sponsor chose not to submit protocols for our review under CVM's generally available protocol review process, except for one study protocol submitted in 2006. That study would have been conducted under FDA's Good Laboratory Practices and would have provided preliminary information about residue depletion (although not the data necessary to establish an R_m), but the sponsor did not submit a report from this study and it does not appear this study was ever conducted.

These decade-long communications, along with the clear requirements of the regulatory text, provided the sponsor with notice of what is needed to meet the statutory requirements as well as ample time to carry out the necessary studies. To date, CVM has not received data demonstrating the approved method is adequate to measure the residue of carcinogenic concern in compliance with the requirements of FDA regulations or that an alternative analytical method would meet such requirements.

CVM, too, has made the swine industry and general public aware of its concerns with the adequacy of the approved method for carbadox. Its concern was discussed in the 2016 NOOH, the 2020 Proposed Order, and during the subsequent public hearing. Indeed, members of the industry and the general public submitted comments to the dockets and made oral presentations at the public hearing. While we take seriously the concept that the sponsor, veterinarians, swine producers, and consumers have relied on the existence of the approved method for carbadox for the last 25 years (and the prior approved method for more than two decades before that) in the form of monetary and physical resource allocation decisions (including inventory decisions on the part of the industry), decisions about animal health, and consumer spending and costs, they have received notice of, and an opportunity to comment on, CVM's concerns and proposed actions. Additionally, were the sponsor to request a hearing in response to the NOOH and point to new or additional data to support the approved method or another approvable method, it may follow that a hearing is granted on that basis and/or that the carbadox NADAs are not withdrawn for that or any other applicable reason. Those considerations together with the considerations discussed throughout this order--including that the larger purpose of an approved method is to protect against the presence of residue of carcinogenic concern in animal tissues consumed by the public--outweigh any such reliance interests.

V. Conclusion and Order

Although CVM previously determined that carbadox and its metabolites, including DCBX, induce cancer in animals, in the January 1998 approval of the supplemental NADA for

carbadox, CVM determined that no such residues of the drug would be found in edible tissues after the preslaughter withdrawal period by the approved method. The failure to establish an R_m (which depends on knowing the relationship between a marker residue and the residue of carcinogenic concern) during the 1998 process, coupled with analysis of new information showing that carcinogenic residues persist longer than previously known, means that the approved method does not meet the requirements of the FD&C Act and the SOM regulations and is inadequate to monitor carbadox residues in compliance with FDA's operational definition of no residue. The new information available since the approval of the January 1998 supplemental NADA reinforces the importance of having an approved method that complies with the SOM regulations.

Nothing submitted to this docket or presented at the public hearing or submitted to Docket No. FDA-2021-N-1326 demonstrates that the approved method is adequate to monitor the residue of carcinogenic concern in compliance with FDA's operational definition of "no residue." No new information was submitted or presented that establishes the relationship between QCA and the residue of carcinogenic concern. Such a relationship must be known in order for the method to determine that there is no residue of carcinogenic concern. In addition, no information was submitted or presented that demonstrates an alternative method is adequate to monitor the residue of carcinogenic concern in compliance with FDA's regulations.

Therefore, FDA is revoking the approved method.

VI. References

The following references are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <https://www.regulations.gov>. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. “Determination of Carbadox as Quinoxaline-2-Carboxylic Residues in Swine Liver and Muscle Tissues after Drug Withdrawal.” Available at <https://www.fda.gov/media/136267/download>.

2. FDA, Freedom of Information (FOI) Summary, NADA 041-061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval January 30, 1998. Available at <https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/308>.

3. FDA, FOI Summary, NADA 041-061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval October 5, 1998. Available at <https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/1673>.

4. Suárez, A.F. and Arnold, D., Addendum to the carbadox monograph prepared by the 36th meeting of the Committee and published in the FAO Food and Nutrition Paper 41/3, Rome 1991, http://www.fao.org/fileadmin/user_upload/vetdrug/docs/41-15-carbadox.pdf.

5. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Carbadox, <https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=2176>.

6. Memorandum to File entitled, “CVM Response to Phibro Animal Health Corporation’s September 18, 2020 Comments on CVM’s July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox” (January 6, 2022).

7. Report from Codex Alimentarius International Food Standards FAO/WHO “Maximum Residue Limits (MRLs) and Risk Management Recommendations (RMRs) for Residues of Veterinary Drugs in Foods, CX/MRL 2-2021,” Carbadox, page 47, <https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https://workspace.fao.org/sites/codex/Standards/CXM+2/MRL2e.pdf>.

8. WHO FOOD ADDITIVES SERIES: 51 CARBADOX (addendum), “Toxicological Evaluation of Certain Veterinary Drug Residues in Food,” prepared by the Sixtieth Meeting of

the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO, Geneva, 2003, <https://iris.who.int/bitstream/handle/10665/42800/924166051X.pdf?sequence=1>.

9. Health Canada, Drug and health products, Veterinary drugs, “List of Maximum Residue Limits (MRLs) for Veterinary Drugs in Foods,” <https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/maximum-residue-limits-mrls/list-maximum-residue-limits-mrls-veterinary-drugs-foods.html> (not listing carbadox as an approved veterinary drug in food).

10. Australian Pesticides and Veterinary Medicines Authority, “Substances Not Permitted for Use on Food-Producing Animals in Australia,” <https://apvma.gov.au/node/11626>.

11. Memorandum to File entitled, “CVM’s review of documents Phibro submitted to Docket No. FDA-2021-N-1326 and presentation at the March 10, 2022 Part 15 Hearing” (October 30, 2023).

12. Memorandum to File entitled, “CVM review of comments on the Zhang Article that Phibro references in the document submitted to the Part 15 Hearing docket under cover letter dated June 9, 2022, and entitled, ‘Phibro Animal Health Corporation’s Reply to the January 6, 2022 “CVM Response to Phibro Animal Health Corporation’s September 18, 2020 Comments on CVM’s July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox’ ”” (October 30, 2023).

13. Zhang, J., W. Qu, Z. Wang, and Y. Pan, “Metabolism and Tissue Depletion of Carbadox in Swine, Broilers, and Rats,” *ACS Agricultural Science & Technology* 2022 2(3), 477-485. Abstract is available at <https://pubs.acs.org/doi/abs/10.1021/acsagscitech.1c00260>. Dated: November 1, 2023.

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